dione **9** (mp 97–98 °C) in 89% yield. Further oxidation of **9** with SeO_2 (dioxane/H_2O 10/1, 70 °C, 6 h) furnished (±)-β-pipitzol (**1a**) (mp 125–126 °C) in 50% yield, which was identical (TLC, IR, 360-MHz ^1H NMR) with an authentic sample kindly provided by Professor P. Joseph-Nathan, Instituto Politecnico Nacional, Mexico. Subjection of the minor diastereomer **6b** to the same sequence of reactions afforded (±)-α-pipitzol (**1b**), also identical with an authentic sample.

In conclusion, we have demonstrated that the intramolecular [4 + 2] tropone–olefin cycloadducts are useful intermediates for the construction of complex ring systems, in this case the cedranoid ring system of (±)-β- and (±)-α-pipitzol (**1a,b**). Extension of this strategy to the syntheses of other ring systems embodied in natural products is under active investigation in our laboratories.

Acknowledgment. We thank the National Science Foundation (CHE-8205144), Eli Lilly and Company, and the Alfred P. Sloan Foundation for financial and material support. High-field (360 MHz) ^1H and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (CHE80-24328); mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (CHE-82-11164).

Registry No. (±)-**1a**, 100761-39-5; (±)-**1b**, 108647-46-7; (±)-**3** (isomer 1), 108647-47-8; (±)-**3** (isomer 2), 108647-48-9; (±)-**5** (isomer 1), 108592-55-8; (±)-**5** (isomer 2), 108647-49-0; (±)-**6a**, 108592-56-9; (±)-**6b**, 108592-57-0; (±)-**7**, 108592-58-1; (±)-**8**, 108592-59-2; (±)-**9**, 108592-60-5.

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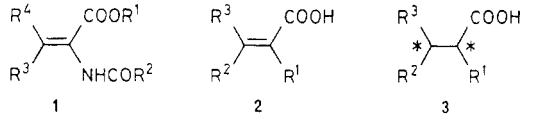
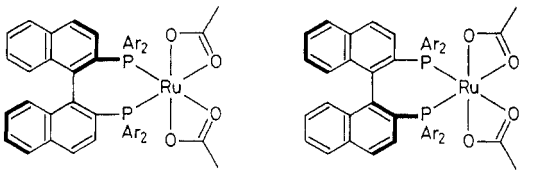
Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Catalyzed by BINAP-Ruthenium(II) Complexes

Summary: Homogeneous hydrogenation of α,β- or β,γ-unsaturated carboxylic acids in the presence of a catalytic amount of Ru[(*R*)- or (*S*)-2,2′-bis(diarylphosphino)-1,1′-binaphthyl](OCOCH$_3$)$_2$ affords the corresponding saturated products in high enantiomeric excesses and in quantitative yields. The new hydrogenation has been applied to the asymmetric synthesis of (*S*)-naproxen, a 1β-methylcarbapenem precursor, and some methylated γ- and δ-lactones.

Sir: Rhodium(I) complexes bearing certain chiral phosphine ligands catalyze the highly enantioselective hydrogenation of unsaturated carboxylic acids or esters of type 1.[1] The extensive, systematic study led to the conclusion that the double-bond geometry and the presence of the α-acylamino group are obligatorily important for the efficiency. Without the amide or related groups, any of the catalyst systems designed so far were unable to give high enantiomeric excesses.[1c] To our knowledge the only exceptional substrate is itaconic acid, an unsaturated dicarboxylic acid being reduced in up to 97.7/2.3 enantioselectivity.[2] We have found that the *ruthenium(II) complexes*[3,4] possessing the BINAP[5] ligand serve as catalyst precursors for the highly stereoselective hydrogenation of a range of substituted acrylic acids lacking the acylamino moiety. With many substrates, the highest enantioselectivities have been recorded.





a, Ar = C_6H_5
b, Ar = p-$CH_3C_6H_4$
c, Ar = p-$CH_3OC_6H_4$

We examined hydrogenation of the olefinic substrates of type **2**, giving **3**, catalyzed by the chiral diphosphine–Ru complexes under varying reaction conditions. All the BINAP–Ru dicarboxylate complexes, **4a–c**, proved to be equally efficient catalysts for the enantioselective transformation. The cationic catalyst system prepared in situ by addition of 2 equiv of fluoroboric acid to the dicarboxylate complex was also effective. A series of experiments using tiglic acid (**2a**) revealed that methanol is the solvent of choice. The optically active dihydro compounds were obtained in nearly quantitative yields by using substrate to catalyst mole ratios (S/C) of 100 to 600. Addition of tertiary amines to the reaction system had little or no effect on the stereoselectivity. The degree of enantioselection is highly affected by hydrogen pressure but the effect depends on the substrates and is not straightforward. The reaction of **2a** preferred low pressure; hydrogenation in methanol using (*S*)-**4a** as catalyst at initial hydrogen pressures of 4 and 101 atm gave the product, (*S*)- **3a**, in 91% and 50% ee, respectively. However, the opposite trend was observed in the reaction of atropic acid

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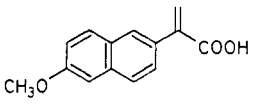
Table I. BINAP-Ru-Catalyzed Asymmetric Hydrogenation of α,β-Unsaturated Carboxylic Acids[a]

	substrate				conditions			product	
	R^1	R^2	R^3	catalyst	substr/cat.	H_2, atm	time, h	% ee[b]	confign[c]
2a	CH_3	CH_3	H	(*R*)-**4a**	160	4	12	91	2*R*
2a	CH_3	CH_3	H	*d*	300	4	12	92	2*S*
2b	H	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3	(*R*)-**4a**	279	101	12	87	3*S*
2c	H	CH_3	C_6H_5	(*R*)-**4a**	590	104	70	85	3*S*
2d	C_6H_5	H	H	(*S*)-**4a**	397	112	24	92	2*S*
2e	H	$HOCH_2$	CH_3	(*R*)-**4a**	145	86	16	93[e]	3*R*
2f	H	CH_3COOCH_2	CH_3	(*R*)-**4a**	106	98	12	95	3*R*
2g	H	$HOCH_2CH_2$	CH_3	(*R*)-**4a**	129	100	12	93[e]	3*S*
2h	H	$CH_3COOCH_2CH_2$	CH_3	(*R*)-**4a**	110	100	12	88	3*S*
2i	CH_3	CH_3COOCH_2	H	(*R*)-**4a**	106	4	12	83	2*R*
2j	$HOCH_2$	CH_3	H	(*S*)-**4a**	145	4	12	95[f]	*g*
5				(*S*)-**4a**	215	135	12	97[f]	2*S*

[a] The reaction was carried out in a 0.05–0.3 M solution of the substrate (0.6–3.2 mmol) in degassed absolute methanol at 15–30 °C. The conversion was 100%. [b] Determined by HPLC analysis of the corresponding amide derived from the product and (*R*)-1-(1-naphthyl)ethylamine. [c] Determined by sign of rotation. [d] Prepared by addition of 2 equiv of HBF_4 to (*S*)-**4a**. [e] The optical purity based on the rotation values of the corresponding lactones: (*S*)-3-methylbutyrolactone (97% ee), $[\alpha]_D$ −24.7° (*c* 4, methanol) (Leuenberger, H. G. W.; Boguth, W.; Barner, R.; Schmid, M.; Zell, R. *Helv. Chim. Acta* **1979**, *62*, 455); (*S*)-3-methylvalerolactone (90% ee), $[\alpha]_D$ −24.8° (*c* 5.6, chloroform) (Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556). [f] Based on ^1H NMR analysis using chiral shift reagent Eu(hfc)$_3$. [g] Not determined. $[\alpha]^{17}_D$ −3.3° (*c* 2.93, methanol).

(**2d**) with the same catalyst producing (*S*)-**3d** in 48% ee at 4 atm and in 92% ee at 112 atm. The substitution pattern including double-bond geometry affects the reactivity together with sense and degree of the asymmetric induction. For example, hydrogenation of *E*-configurated **2a** with (*R*)–**4a** (methanol, 4 atm, 12 °C) afforded (*R*)-**3a** in 91% ee, whereas the *Z* isomer, angelic acid, was reduced rather sluggishly to give the *S* enantiomer in 57% ee (100% yield at 125 atm). Even 2,3-dimethyl-2-butenoic acid, a fully substituted olefinic substrate, was hydrogenated ((*R*)-**4a** catalyst, S/C 585, 134 atm) with fair (*R*/*S* = 85/15) enantioselectivity. Hydrogenation of geranic acid (**2b**) proceeded in a regioselective manner to give citronellic acid, leaving the C(6)–C(7) double bond intact. Thus, as summarized in Table I, the BINAP–Ru complexes exhibit a high level of enantio-differentiating ability in the reaction of prochiral acrylic acids having various alkyl and aryl substitution patterns. The optical purities of the hydrogenation products can be further enhanced by recrystallization of their appropriate salts.

The synthetic significance of this asymmetric catalysis is obvious. For instance, (*S*)-naproxen [(*S*)-**6**)], a useful antiinflammatory agent,[6] was readily obtainable by the asymmetric hydrogenation of **5** with (*S*)-**4a** as catalyst. Usual workup and distillation of the product under reduced pressure afforded (*S*)-**6** in 92% yield and in 97% ee, $[\alpha]_D^{25}$ +64.2° (*c* 1.03, chloroform). The hydrogenation of **7** with (*R*)-**4a** (S/C 100, 100 atm) afforded **8**, an important intermediate for synthesis of 1β-methylcarbapenems,[7] with 87:13 diastereoselectivity. The utility of the reaction has become more general by extension of the substrates to include various oxygen-functionalized unsaturated carboxylic acids, **2e–j** (Table I). The optically active hydroxy acids or the corresponding lactones such as **9–11** are useful building blocks for natural product syntheses but not readily accessible.[8] The observed sense of asymmetric induction is identical with that of the substrates without the oxygen functionalities, indicating that the carboxyl moiety, and not other oxygen-containing groups, is directing the stereoselective reaction.



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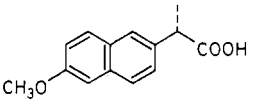
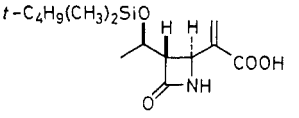


(S)-**6**



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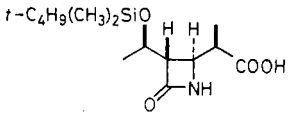

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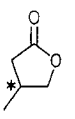

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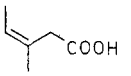

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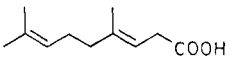

13

Certain β,γ-unsaturated carboxylic acids were also hydrogenated in an enantioselective manner. For example, reaction of **12** (S/C 240, 4 atm) or **13** (S/C 150, 50 atm) catalyzed by (*S*)-**4a** afforded the corresponding (*R*)-3,4-dihydro acids in 88% (^1H NMR of the methyl ester with Eu(hfc)$_3$) and 81% ee (HPLC of the (*R*)-1-(1-naphthyl)-ethylamide), respectively.

Thus the success of the enantioselective hydrogenation of the nonamide olefinic substrates relies on the carboxylate carrying ability of the Ru catalysts. Attempted hydrogenation of the methyl tiglate under the standard conditions resulted in recovery of the starting material.

Acknowledgment. We thank Sankyo Co. for a generous supply of **7** and Mr. I. Kasahara for carrying out the hydrogenation of **13**. H. T. gratefully acknowledges partial support of this work by the Ministry of Education, Science and Culture, Japan and the Naito Science Foundation.

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Supplementary Material Available: Descriptions of the general procedures of the asymmetric hydrogenation and determination of the enantiomeric excesses of the products (2 pages). Ordering information is given on any current masthead page.

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Spiro Asymmetric Induction. 3. Synthesis of Optically Pure Syn or Anti α,β-Dihydroxy Esters by the Aldol Condensation of Chiral Glycolate Enolates†[1]

Summary: The diastereoselectivity of the aldol condensation of the chiral glycolate enolates **1** and **2** is metal-tunable, providing either syn or anti adducts **3–6**. Ethanolysis of these adducts then provides any stereoisomer of the α,β-dihydroxy esters **7–10** in optically pure form.

Sir: Polyhydroxylated carbon compounds are often important biological substances, exemplified by the carbohydrates. As rare or unnatural target molecules of this type become more important,[2] synthetic methods for their assembly become more desirable. As part of a program aimed at the de novo total synthesis of carbohydrates[3] as well as other highly oxygenated natural products, we report a stereoselective route to optically pure α,β-dihydroxy esters based on the aldol condensation of chiral glycolate enolates of **1** and **2**.[4-6] A retrosynthetic analysis of the carbohydrate problem then reduces to iterative aldol condensations, as outlined in Scheme I.[7] In this paper, we report that any one of the four possible stereoisomers of an α,β-hydroxy ester may be prepared in a rational manner.

We have recently reported a route to *S* or *R* α-hydroxy esters based on the highly diastereoselective alkylation of chiral glycolate enolates **1** and **2**, providing 100% optically pure materials after hydrolysis of the dioxolanones and recycling of the chiral auxilliary.[1a] Aldol condensations of these same enolates have been found to be extremely facially selective. The enolate of **1** reacts with various aldehydes to give products **3** and **4**, which result from attack on the *si* face of the enolate, producing the 2*S* stereochemistry (Table I).[8] No 2*R* products resulting from attack on the *re* face were detected. In a similar fashion, enolate **2** affords complete diastereofacial selectivity, providing the 2*R* stereochemistry in adducts **5** and **6** as a result of *re* face attack on the enolate. Again, no contamination with adducts resulting from *si* face attack were detected. Hence, the chiral enolates of **1** and **2** provide a highly enantioselective entry into either the 2*R* or 2*S* manifolds.

Examination of Table I shows that aldol diastereoselectivity may often be controlled to a large extent by selection of an appropriate enolate counterion. In general, lithium and magnesium counterions provide the anti aldol adducts **3** or **5**. This selectivity is consistent with previous work on the aldol condensations of cyclic *E* enolates.[9] In

† Dedicated to Professor Ernest L. Eliel on the occasion of his 65th birthday.

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(7) Heathcock[5c] has examined such an approach to racemic carbohydrates based on the aldol condensation of lactate enolates. For a related approach, see: (a) David, S.; Lepine, M.-C.; Aranda, G.; Vass, G. *J. Chem. Soc., Chem. Commun.* **1976**, 747. (b) David, S.; Lepine, M.-C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1262.

(8) All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, and elemental analysis or high resolution MS. **General procedure for the aldol condensation**: LDA (1.2–1.5 equiv, generated from *n*-BuLi/hexane and diisopropylamine) in dry THF (0.5 mL/mmol) was cooled to −78 °C. A solution of the desired dioxolanone **1** or **2** (1 equiv) in THF (0.3 mL/mmol) was added dropwise. After stirring for 10–20 min, 1 equiv of another metal source ($MgBr_2$ or Cp_2ZrCl_2) was added if desired. After stirring 30 min, the aldehyde (1.5–2.0 equiv) was added. Reaction was usually complete within 30–60 min (TLC analysis). Aqueous workup (ether/saturated sodium bicarbonate) followed by drying ($MgSO_4$), evaporation, and flash chromatography gave the pure isomeric aldol adducts. In all cases, only two isomers were obtained. These could be separated by radial chromatography (1 mm thick silica gel) with 5–10% ethyl acetate hexane or by semipreparative HPLC (Rainin Dynamax silica gel column) with 15% ethyl acetate/hexane. **General procedure for dioxolanone ethanolysis**: Anhydrous hydrochloric acid was bubbled through a solution of dioxolanone **3–6** in absolute ethanol (4 mL/mmol) at a moderate rate for ca. 2 min at room temperature. The solution was then refluxed for 2 h, cooled, poured into saturated sodium bicarbonate, and extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography over silica gel with ca. 40% ethyl acetate/hexane provided the pure α,β-dihydroxy esters **7–10**.

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